Official Title: A Phase I Trial of Tolcapone Alone and in Combination With Oxaliplatin in Patients With Relapsed or Refractory Neuroblastoma
IRB-Approved Date: 5/17/16
NCT02630043

Patient name

DOB

MRN

Physician

FIN

Permission to Take Part in a Human Research Study & HIPAA Authorization for Release of Health Information for Research Purposes

Title of research study: A Phase I Trial of Tolcapone alone and in Combination with Oxaliplatin in Patients with Relapsed or Refractory Neuroblastoma or Medulloblastoma

Sponsor: The Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC) at Spectrum Health

Investigator: Dr. Jessica Foley, MD

"You" refers to the subject.

"You" refers to you and your child.

"We" refers to Helen DeVos Children's Hospital

You are being invited to participate in a research study conducted by the Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC). The NMTRC is a collaboration of academic medical centers and other organizations around the country. Helen DeVos Children's Hospital, a member of Spectrum Health Hospitals, serves as the lead organization of the NMTRC.

You are being invited to take part in this research study because you have a cancer called neuroblastoma or medulloblastoma, and your cancer did not respond to previous therapy, or the cancer has come back.

After reading and discussing the information in this consent form, you should know:

- Why this research study is being done
- What will happen during the study
- Any possible benefits to you
- The possible risks to you
- Other options you could choose instead of being in this study
- How your personal health information (PHI) will be treated during the study and after the study is over
- Whether being in this study could involve any cost to you
- What to do if you have problems or questions about this study

What should you know about a research study?

- Someone will explain this research study to you.
- You volunteer to be in a research study.
- Whether or not you take part is up to you.
- You can choose not to take part in the research study.
- You can agree to take part now and later change your mind.
- Whatever you decide it will not be held against you.
- Feel free to ask all the questions you want before you decide.

Who can you talk to?

If you have questions, concerns, or complaints, or think the research has hurt you in any way, you may talk to the investigator or members of the research team at [redacted].

This research has been reviewed and approved by the Spectrum Health Institutional Review Board. You may talk to them at [redacted] or [redacted] for any of the following:

- Your questions, concerns, or complaints are not being answered by the investigator or research team.
- You cannot reach the investigator or research team.
- You want to talk to someone besides the investigator or research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

Why are we doing this research?

The purpose of this research study is to evaluate an investigational drug (Tolcapone) alone and in combination with oxaliplatin, for relapsed and refractory neuroblastoma and medulloblastoma. Tolcapone is approved by the U.S. Food and Drug Administration (FDA) for adults, but is an investigational drug in this study because it has not been approved in pediatrics for this indication. Oxaliplatin, although a drug approved by the FDA for other cancers, is investigational for treatment of neuroblastoma and medulloblastoma in this study. This study will look at the safety and tolerability of tolcapone in combination with oxaliplatin as well as the tumors response to this study drug.

This study is a Phase I trial. A phase I trial is a trial that is in the first stage of testing in human subjects. The purpose of a Phase I study is to test for safety and to find the highest dose of the drug that subjects can tolerate (optimal dosing). Optimal dosing of tolcapone in combination with oxaliplatin in pediatric patients is not known at this time. This is the first time tolcapone has been given to children. Read the sections on risks and benefits carefully and be sure you understand them.

How long will I be in the research?

Study treatment will be given to you in five 21-day cycles. This calculates to 105 days, or 15 weeks, or about 3.5months. You may continue this until you have progression, you no longer wish to continue, or your study doctor decides it is not in your best interest. If you continue on drug past the five 21-day cycles, you will still be considered part of the study. After you are finished taking tolcapone, you will then be followed to see how you are doing every 3 months for one year, then yearly until 5 years after stopping the study drug.

How many people will be studied?

We expect about 10-16 people here will be in this research study out of 42 people in the entire study nationally (or internationally).

What happens if I say yes, I want to be in this research?

Subjects signing this consent form will be given Tolcapone, a drug that has not previously been used in children, both alone and in combination with oxaliplatin.

This study is a Phase I trial. A phase I trial is a trial that is in the first stage of testing in human subjects. The purpose of a Phase I study is to test for safety and to find the highest dose of the drug that subjects can tolerate (optimal dosing). Optimal dosing of Tolcapone in pediatric patients is not known at this time. This is the first time Tolcapone has been given to children. Read the sections on risks and benefits carefully and be sure you understand them.

This study will be using increasing doses that will continue until unacceptable toxicities (side effects) are identified. If there is a toxicity in one group of subjects, that dose may be repeated. There will be a hold in enrollment after each 3 subjects (each cohort) are enrolled in order to monitor that dose for safety and toxicities. All children will receive the same dose of oxaliplatin.

Because of the way subjects are enrolled, there is a possibility that even if you qualify for this study, there may not be a space available for you to start on study. You may receive a different dose of Tolcapone than other subjects depending on when you start on study. We cannot guarantee the dose that you will be given until you start on the study. Both you and the study doctor will know what dose you receive. The dose you receive may be so low that it has no effect or so high that you have side effects you cannot tolerate.

Screening:

You will undergo a number of standard tests and research-related procedures before being able to enroll in this study. You will need to have the following exams, tests and procedures to find out if you can be in the study. The results of these studies may show that you are not eligible to take part in this study. Most of these exams, tests and procedures are part of regular neuroblastoma care and may be done even if you do not join the study. Some procedures are being done only for research purposes as part of this study. Those tests are also listed below. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

Tests to be performed within 5 days of starting study:

- Medical history
- Physical exam
- Vital signs (blood pressure, pulse, temperature)
- Blood tests
- Urine tests (including a pregnancy test for girls who can become pregnant {age 13 or greater, or has started menstruation})

Tests to be performed within 21 days of starting study:

- MRI or CT scan of the tumor(s)
- Any other imaging studies or tests deemed necessary for assessing your tumor by your treating physician
- MIBG or PET scan if you have neuroblastoma. An MIBG scan involves injecting a radioisotope into the blood on the first day, and then scanning the whole body on the second day to see where the isotope was absorbed.
- Patients with suspected bone marrow involvement only- Bone marrow aspirations and examination (this involves using a needle to extract a small amount of your bone marrow from both of your hips usually under anesthesia; at the time of your procedure you will be asked to sign a consent form for the anesthesia). We will ask you if we can collect a small amount of additional bone marrow that will be used for special research testing of neuroblastoma cells if they are present. (There is a separate consent for this at the end of this form.)

Tests to be performed for research related purposes only include:

- Additional samples of your Bone marrow aspirations as noted above (additional samples are voluntary)
- Additional samples of your blood (additional samples are voluntary)
- If you have a tumor biopsy or surgical resection as part of your standard of care we would ask if we can collection additional samples of your tumor (additional samples are voluntary).
- As part of this study you will have extra research-related blood tests done called pharmacokinetic studies. The pharmacokinetic studies will involve having additional blood samples drawn on Day 1 and Day 8 of the study. You will have blood drawn at 7 (seven) specific intervals on Day 1 and Day 8 of Cycle 1. Having these blood samples done will add approximately 4 to 6 extra hours to your clinic visit. These blood samples will be tested in a laboratory to determine the level of Tolcapone in the blood. This information will be used to better understand the metabolism (break down) of Tolcapone in children. Whenever possible, these samples will be obtained from a central venous line.

Study Treatment:

Study treatment will be given to you in five individual cycles (courses) of therapy. Each course of therapy lasts 21 days; this is what we call a “cycle”. Each cycle will occur immediately after the last. This means that since each cycle is 21 days long, on day 22 you will be starting the next cycle.

If the exams, tests and procedures show that you can be in the study, and you choose to take part, tolcapone will be started in clinic on Day 1. You will take tolcapone orally, by mouth, two or three times a day depending on which dose you are assigned to. Tolcapone will be provided to you as a tablet. You must be able to swallow tablets to participate on this study.

You will be in clinic on this first day for approximately 6 to 8 hours. After this, you will be given the tolcapone to take home and you will take it each day as prescribed for as long as you are in this study, unless you have side effects from the medicine or your tumor worsens. You will return to clinic on days 8 and 15 of the first cycle for a physical exam, blood draw, and to discuss any side effects of the medication you may be having. The Day 8 visit will last about 6-8 hours and the Day 15 visit will last about 2 hours.

Starting in cycle 2 for patients with neuroblastoma that does not have CNS (brain and/or spine) involvement, and in Cycle 3 for patients with any CNS neuroblastoma involvement or any medulloblastoma patients, oxaliplatin will be given to you intravenously (IV) on Day 1 of each cycle. Additionally, you will continue to take the tolcapone as prescribed.

At the beginning of each new cycle you will have some of these tests repeated including:

- Medical history
- Physical exam
- Vital signs (blood pressure, pulse, temperature)
- Blood tests
- Urine tests (including a pregnancy test for girls who can become pregnant)
- Any other imaging studies or tests deemed necessary for assessing your tumor by your study doctor

Additionally at the end of cycles 1, 3, and 5 you will also have the following procedures repeated:

- MRI or CT scan of the tumor(s)
- MIBG or PET scan.
- Bone marrow aspirations and examination if your bone marrow was positive for disease at enrollment (We will ask you if we can collect a small amount of additional bone marrow that will be used for special research testing of neuroblastoma cells if they are present. There is a separate consent for this at the end of this form.)

If your cancer is responding and if you are not experiencing unacceptable side effects from treatment, it will be up to your study doctor's discretion to continue treatment on protocol beyond the five 21-day cycles of treatment described above (you may continue this until you have progression, you no longer wish to continue, or your study doctor decides it is not in your best interest). If you continue on drug past the five 21 day cycles, you will still be considered part of the study and you will still need to have procedures done with every cycle as explained above. These follow ups include the same tests and procedures as the preceding cycles did. We will also continue to collect information from these tests and procedures and on your treatment and outcomes.

As a part of your treatment you may have a surgical operation to remove as much of the tumor as possible. You will be asked by the pediatric surgeon to sign a separate surgical consent form, which will review the risks of that surgical procedure. If the tumor is obtained by surgery for routine (non-study) care, you will be asked if some of the tumor can be saved for special research testing of cancer cells if they are present. There is a separate consent for this at the end of this form.

After you are finished taking tolcapone, the study doctor will ask you to visit the office for a follow-up visit about 30 days after your last dose of tolcapone. During this follow up visit you will discuss any side effects you may still be having. You will then be followed to see how you are doing every 3 months for one year, then yearly until 5 years after stopping the study drug. We will do this follow up either by phone or e-mail.

All required radiology scans (MIBG's, PET's and MRI/CT's), must be done at the study institution, Helen DeVos Children's Hospital, unless otherwise approved by the sponsor. If Helen DeVos Children's Hospital is not your home institution, all other care (excluding the previously mentioned) can be done at your home institution at the discretion of your study doctor.

Methods for Providing/Administering Study Drug
Tolcapone will be taken orally (by mouth) every day that you are on the study. Tolcapone is a tablet that will be supplied to you.

Oxaliplatin will be given intravenously (by IV) once a day on day 1 of each 21 day cycle starting in Cycle 2 or cycle 3.

You will be asked to keep a daily diary of the study drug and dose you are taking; this diary will be provided to you by the study doctor, and will need to be returned to the study doctor at the end of each cycle.

Throughout the study, you will be asked to report any difficulties or side effects that you experience, regardless of whether or not you feel they are related to, or caused by, the study medication. It is very important for you to discuss any difficulties or side effects with your study doctor.

If you have any significant side effects or problems, you should promptly contact your home treating oncologist. Your home treating oncologist will then decide if you should come in to the hospital. In addition you will need to contact your study doctor. Your study doctor will determine what you should do about your study drug doses. Doses may be reduced, delayed or omitted if you have toxicities or side effects. If your condition worsens during the study, your study doctor may remove you from the study.

While you are on this study, there are certain medications and treatments that you will not be allowed to take. Those include any other cancer killing agents or chemotherapy, any other investigational (study) drugs, immunotherapy, hormonal therapy, and targeted therapies. Please discuss all medications that you are currently taking or wish to take with your study doctor.

PROCEDURES AND ASSESSMENTS FOR THIS STUDY

	Screen	Cycle 1				Cycles 2 through 5			Subsequent Cycles	5 year Follow Up
		Day 1	Day 8	Day 15	Day 21	Day 1	Day 8	Day 21	Day 1	
Informed consent	X									
Medical History	X									
Interval Medical History & Physical Exam		X	X	X		X	X		X	
Vital signs	X	X	X	X		X	X		X	
Bloodwork	X	X	X	X		X	X		X	
Pregnancy test (urine or blood)	X					X			X	
Urine Tests	X	X				X			X	
Administration of Oxaliplatin						X[d]			X	
Administration of Tolcapone		→	→	→	→	→	→	→	→	
CT or MRI	X				X			X[a]	X[a]	
MIBG or PET scan[e]	X				X			X[a]	X[a]	
Bone Marrow aspirate and biopsy[b e] *(if + at enrollment)*	X				X			X[a]	X[a]	
Pharmacokinetic Blood Samples		X	X							
Optional Blood Samples	X									
Survival Call or E-mail										X[C]

[a] *At the end of cycle 3 and 5 then per standard of care in subsequent cycles (minimum every 3 cycles)*

[b] *Standard of Care Bone Marrow. (Separate consent required for additional research samples)*

[c] *Survival Follow-up will occur 30 days after stopping Tolcapone. After that we will contact you every 3 months for the first year and then yearly for 5 years.*

[d] *Starting in Cycle 2 for neuroblastoma without CNS disease and in Cycle 3 for medulloblastoma and neuroblastoma with CNS disease.*

[e] *for neuroblastoma patients only*

SUBJECT/FAMILY RESPONSIBILITIES

If you wish to take part in this study, we expect that you will:

- Keep your study appointments. If you cannot keep an appointment, contact your study doctor or research study staff to reschedule as soon as you know that you will miss the appointment.
- Take your Tolcapone as directed. Document all your doses on the drug diary, including missed doses.
- Tell us about any medications you are taking- including any homeopathic remedies or nutritional supplements- so we can check how the drug being studied and your medications may interact. If you need to start on any new medications while you are in the study, please check with your study doctor before you do so.
- Tell us about any side effects, doctor visits, or hospitalizations that you may have, whether or not you think they are related to the study therapy.

What happens if I say no, I do not want to be in this research?

You may decide not to take part in the research and it will not be held against you. A refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled.

What happens if I say yes, but I change my mind later?

You can agree to take part in the research now and stop at any time it will not be held against you.

Discontinuing participation will not result in penalty or loss of benefits to which you are otherwise entitled.

If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether the investigator can continue to collect data from your routine medical care. If you agree, this data will be handled the same as research data.

Could being in this study be bad for me?

You may have side effects while on the study. Everyone taking part in the study will be carefully watched for any side effects. However, study doctors do not know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study drug. In some cases, side effects can be serious, long lasting, may never go away, or may even cause death. You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks of Tolcapone:

This is the first time tolcapone has been given to children. Therefore, the risks of tolcapone are not known in the pediatric population. That is one reason that this study is being done.

From the adult studies on Tolcapone, the following risks were seen:

Common Happens to 10-51 patients out of every 100	**Less Common** Occurs in to 4-10 patients of every 100	**Rare** Happens to fewer than 4 patients out of every 100
• Nausea • Diarrhea • Anorexia (decreased appetite) • Dyskinesia or dystonia (impairment of voluntary muscle movement) • Drowsiness or somnolence • Orthostatic hypotension (low blood pressure resulting in light-headed or dizziness feeling when moving from sitting to standing)	• Syncope (temporary loss of consciousness caused by low blood pressure) • Vomiting • Constipation • Dry mouth • Abdominal pain • Urinary tract infection • Blood in urine • Upper respiratory infection • Increased perspiration (sweating)	• Hepatocellular (liver) damage/hepatotoxicity • Chest pain • Palpitation • Loss of balance, weakness, or stiffness • Agitation, feelings of discomfort, panic, or irritability • Euphoria • Hyperactivity • Mental deficiency • Fever • Depression • Hypoesthesia (reduced sense of touch) or tingling • Tremor • Speech disorder • Vertigo • Hair loss

• Vivid dreaming • Dizziness or confusion • Headache • Hallucinations (reported primarily in patients > 75 years old)		• Bleeding • Rash • Indigestion • Flatulence (gas) • Urine discoloration or disorder • Tumor, uterine tumor • Incontinence • Increase in transaminase levels • Excessive or reduced muscle movement due to muscle rigidity or loss of control • Arthritis • Neck pain or muscle pain • Rhabdomyolysis (destruction of striated muscle cells) • Cataracts or eye inflammation • Tinnitus (ringing in ears) • Difficulty breathing • Sinus congestion • Bronchitis or pharyngitis • Influenza • Burning • Flank pain • Injury or infection

It is important to know that there have been rare cases of fatal liver failure reported in adult patients treated with tolcapone. It is unknown whether the risk of liver damage will be higher when tolcapone is administered in pediatrics or in combination with oxaliplatin.

It is also important to know that two neuroblastoma patients with CNS (brain) disease that have been enrolled on this study to date have experienced intratumoral hemorrhage in these lesions. The bleeding was experienced throughout treatment with tolcapone alone and during the combination of tolcapone and oxaliplatin. One of these patients experienced significant thrombocytopenia and developed an intracranial hemorrhage that led to death. It has been well documented in neuroblastoma CNS lesions that intratumoral bleeding can occur in these tumors, this has been show in many past studies with different therapies. This subject's intracranial hemorrhage was unlikely related to tolcapone but was possibly related to the treatment effect.

The chance of having side effects and the severity of side effects may increase with higher doses of tolcapone. All subjects will be monitored closely and will be evaluated for any signs of early side effects.

Certain other drugs may interfere with Tolcapone. Please check with the study doctor before starting ANY new medication or treatment.

Risks of abrupt withdrawal of Tolcapone: Some adult patients taking tolcapone experienced confusion, fever, and muscle rigidity when they abruptly stopped taking tolcapone. Due to this potential side effect we recommend you talk to your study doctor before you plan to stop taking the drug and they will advise you on how to stop taking it safely.

Risks and side effects related to <u>Oxaliplatin</u> include those which are:

Common Happens to 10-65 patients out of every 100	**Less Common** Happens to 3-10 patients out of every 100	**Rare** Happens to fewer than 3 patients out of every 100

• Numbness or tingling sensation of mouth, throat, arms, legs, fingers, and toes, which may become worse with cold temperatures and which may affect the ability to perform tasks that require fine muscle coordination.
• Nausea and vomiting
• Stomach cramps or pain
• Diarrhea or constipation.
	• Headache
	• Runny nose
	• Feeling of "heartburn"
	• Change in taste
	• Dehydration (fluid loss)
	• Dizziness and/or loss of coordination
	• Feeling of extreme tiredness not relieved by rest or sleep
	• Reddening and cracking of the skin on the hand palms and soles of the feet, associated with pain and possibly infection
	• Sudden reddening of face and neck
	• Rash
	• Difficulty sleeping
	• Loss of appetite or desire to eat
	• Allergic reaction that may be life threatening
	• Shaking chills
	• Blood in the urine
	• Painful or difficulty urinating
	• Inflammation of the vein through which the drug was given
	• Fewer white blood cells, red blood cells, and platelets in the blood
	  ○ Low number of white blood cells increase risk of infection
	  ○ Low number of red blood cells can cause fatigue
	  ○ Low number of platelets increases bruising and bleeding
	• Nose bleed
	• Loss of weight
	• Soreness or ulcers inside the mouth and throat
	• Hair loss
	• Swelling of hands, arms, feet, and legs
	• Joint pain
	• Lung infection
	• Sore throat
	• Fever
	• Increased levels of creatinine in blood, which could indicate kidney damage
	• Lower levels of measured salt (potassium) in blood.
	• Too much acid in the blood
	• Hiccups
		• Shortness of breath
		• Sudden, temporary feeling of difficulty in swallowing or breathing which can occur during or shortly after the infusion and may be caused by swallowing a cold drink
		• Infections
		• Irregular or rapid heart beat
		• Rare but serious damage to the liver, which can lead to an enlarged liver and spleen, bleeding from the veins in the esophagus, a yellow appearing skin, and fluid collection in the abdomen which makes your abdomen look distended
		• Tissue irritation or damage, which may be severe if drug leaks from injection site causing pain, redness, and swelling.
		• Severe allergic reaction, which can be life threatening with shortness of breath, low blood pressure, and a rapid heart rate.
		• Blood clots
		• Blurred vision or blind spots in vision.
		• Damage to lung tissue
		• Damage to kidney (potentially permanent)
		• Loss of some hearing
		• A bleeding disorder that can cause bleeding from many areas of the body, including the nose, rectum, and in urine

	• Too much gas produced in intestines • Difficulty swallowing • Mild increases in liver enzymes without symptoms and usually returning to normal • Increase in blood pressure • Inflammation of the ear • Inflammation of the small bowel, causing pain or discomfort • Depressive feelings • Cough • Bone Pain • Inability to urinate • Damage to the surface of the eye, leading to pain or tearing • Restless involuntary movement	• Blockage of the intestine (may require treatment) • Inflammation of the pancreas, potentially causing severe abdominal pain.

Please talk to your study doctor before starting any new medications or herbal supplements and before making a significant change in your diet.

Risks of Blood Draws:
Risks associated with drawing blood are slight, but some risks include: pain, excessive bleeding, fainting or feeling lightheaded, bruising, infection (a slight risk any time the skin is broken), and multiple punctures to locate veins.

Blood will be drawn from a central line whenever possible to minimize these risks.

MRI
The MRI may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the MRI. Temporary hearing loss has been reported from this loud noise. You may be asked to wear ear protection. At some time during the test, you may be asked to hold your breath for a while, which can be uncomfortable.

CT Scan or PET Scan
A CT Scan exposes you to radiation. No amount of radiation is safe, and exposure adds up over a lifetime. The total dose of radiation from a CT scan is about three times the amount of radiation you would normally be exposed to in one year ("background radiation"). The amount of radiation can vary depending on the part of the body that is being examined. If you have more procedures that expose you to radiation, your risk will go up. Risks of harm include getting a cancer, or changes to your genes. Your risk of harm may be as high as 1 in 1,000. Your study doctor can discuss this with you in more detail.

Risks of Bone Marrow Aspiration:
During this study, a sample of bone marrow will be collected from your hip bone(s) for testing (occasionally another bone is selected); this is usually done under anesthesia. Once you are under the anesthesia, a special needle will be inserted into the bone to collect the marrow. Pressure may be felt as the needle is inserted into the bone. There is a sharp sucking sensation as the marrow is aspirated, which lasts for only a few moments. There may be

some bleeding at the puncture site. You may experience discomfort or pain. More serious risks, such as serious bleeding or infection, are very rare.

Reproductive Risks:
Because the study drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. Girls who can become pregnant (age 13 or older or have started having menses) who enter the study must have a negative pregnancy test prior to entry and during the study. Additionally, the effects on sperm are not known. If you are a girl who can become pregnant or a male able to father children, you must use an acceptable method of birth control during the study to prevent pregnancy.

Both men and women should use one of the more effective birth control methods during treatment and for 90 daysafter treatment is stopped. These methods include

- total abstinence (no sex),
- oral contraceptives ("the pill"),
- an intrauterine device (IUD),
- levonorgestrol implants (Norplant), or
- medroxyprogesterone acetate injections (Depo-provera shots).

If one of these cannot be used, contraceptive foam with a condom is recommended. Talk to your study doctor to decide what type of birth control is acceptable.

A possible side effect of this study is sterility (inability to have children).

If you suspect that you have become pregnant during this study, you must notify the research team immediately. You will be withdrawn from the study if you become pregnant.

For more information about risks and side effects, ask your study doctor.

You will be informed as additional information is discovered about how the study drug may affect the risk and/or your willingness to continue to participate in this study. Your study doctor will inform you of all known risks; however, there may be physical, mental or genetic adverse risks that are not known at this time.

What if there are new findings?
We will tell you if we learn any new information that may affect your health, welfare, or decision to stay in this study. You may be asked to sign a revised consent form if this occurs.

Will I need to pay for any of the tests or procedures in the study?
Taking part in this study may lead to added costs to you or your insurance company. Your study doctor will discuss any expected added costs that may be billed to you or your insurance provider. Participating in this study requires that you visit the study hospital, Helen DeVos Children's Hospital, multiple times over the course of the full study for evaluations (physical exam, blood draw, urine analysis, etc.) and scans (MRI/CT, MIBG/PET).

The study drug, tolcapone, will be provided free of charge by the NMTRC, while you are participating in this study. However, even though it is unlikely, there is a possibility that the supply of study drug may run out. If this happens, your study doctor will talk with you. You may have to be taken off study. Or, if the drug becomes commercially available, you may be able to obtain additional drug from the manufacturer and you or your insurance may be asked to pay for it.

You or your insurance company will be charged for continuing standard medical care and/or hospitalization. You or your insurance company will be responsible for charges for other drugs (including the oxaliplatin), hospitalizations, clinic visits, x-rays, lab tests, etc.

You might have unexpected expenses from being in this research study. These charges may be submitted to your health insurance. However, your health insurance may not pay these charges because you are in a research study. If your insurance company requires any co-payment or deductible, you will be responsible for making that payment. In addition, if you are injured as a direct result of being in this study your insurance company may not pay to treat these injuries. Ask the study doctor for more information about this. We also encourage you to determine your health insurer's policy about paying for treatment in a research study.

Participating in this study requires that you visit the study hospital Helen DeVos Children's Hospital multiple times over the course of the full study for evaluations (physical exam, blood draw, urine analysis, etc.) and scans (MRI/CT, MIBG/PET).

Will being in this study help me in any way?

Taking part in this study may or may not make your health better. While benefit is possible, participation may not benefit you and your health could worsen during this study.

We do know that the information from this study will help doctors learn more about tolcapone as a treatment for cancer. This information could help future cancer patients.

What other options are there?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no specific treatment
- You can receive oxaliplatin off-study without receiving tolcapone
- If you decide that you don't want any more active treatment, one of your options is called "comfort care." Comfort care includes pain medication and other support. It aims to maintain your comfort and dignity rather than cure disease. Usually this care can be provided at home.

You should talk to your home treating oncologist about your choices before you decide if you will take part in this study.

What happens to the information you collect?

We will do our best to make sure that your personal medical information will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law.

If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Each subject in this trial will be identified by a unique identifier that will be used on all report forms and any other material submitted to the NMTRC. Report Forms for this study will be both paper and electronic. Electronic data will be stored in a secure data center. Your medical records are available to those caring for you at this hospital. Other people or groups who may see or copy your medical record because you are participating in this study include:

- The investigator and her research staff
- The Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC), affiliates of the NMTRC, and the NMTRC011 study committee
- Spectrum Health Hospitals and its affiliates
- The Spectrum Health Institutional Review Board (IRB) and staff
- Valeant Pharmaceuticals and their affiliates
- The U.S. Food and Drug Administration
- The Western Institutional Review Board® (WIRB®)
- The Spectrum Health Institutional Review Board
- Department of Health and Human Services (DHHS) agencies

Some of these organizations may be given direct access to your medical records for verification of the research procedures/data involved. By signing this document you are authorizing this access.

Otherwise your name and other medical information that identifies you will not be released without your written permission, unless required by law. If results of this study are published, your identity will remain confidential.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Federal law provides additional protections of your personal information. These are described in a later section. Please refer to the separate authorization (HIPAA) form that explains more specifically how your personal health information will be used.

Can I be removed from the research without my OK?

Your study doctor or the sponsor may decide to take you out of the study at any time without your consent if any of the following occur or for other reasons:

- You do not meet the criteria to take part in the study.
- The side effects of the study drug are too harmful for you.
- You need a treatment that is not allowed on this study.
- Your tumor worsens.
- You become pregnant.
- The study doctor believes it is in your best interest.

- New information becomes available that would suggest that continuing in this study would not be in your best interest.
- You do not consent to continue in the study after being told of changes in the research that may affect you.
- The study is stopped.
- Or for any other reason.

The Neuroblastoma and Medulloblastoma Translational Research Consortium, Spectrum Health Hospitals, Valeant Pharmaceuticals, Western Institutional Review Board, or the FDA has the right to stop this study at any time. They may stop the study without your agreement based on medical information available to them.

If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether the investigator can continue to collect data from your routine medical care. If you agree, this data will be handled the same as research data.

What if I'm injured or made sick from the research?

Participating in research may result in an injury or illness. Medical treatment related to an injury or illness will be available at your treating institution, but such treatment may not be free of charge. No funding has been set aside to pay for the costs of treating an injury or illness that results from this study. Your medical insurance may pay for such treatment, but you may ultimately be billed for payment.

Ask the study doctor for more information about this. We also encourage you to determine your health insurer's policy about paying for treatment in a research study.

By signing this consent form, you are not giving up any legal rights.

What else do I need to know?

You will not be paid for taking part in this study.

HIPAA Authorization for Release of Health Information for Research Purposes

The information we are asking to use and share is called Protected Health Information (PHI). It is protected by a federal law called the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). In general, we cannot use or share your health information for research without your permission.

What will be done with my information?

Your health information will be collected and entered in a database along with the information from other people taking part in this study.

Why am I being asked to release it?

Your health information will be collected and entered in a database along with the information from other people taking part in this study.

What will be released?

To complete this research study, we will need to collect and release (disclose) information about you. This information may include:

- Your date of birth, name, contact information, social security number, medical record number, and insurance information.
- Existing medical records and medical history.
- New health information collected for purposes of this study.

Who will use it or share it?

- The investigator and her research staff
- Spectrum Health staff or its agents
- The Spectrum Health Institutional Review Board (IRB) and its staff
- The Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS)
- National Institutes of Health (NIH)
- The Sponsor(s) of the research, NMTRC, or its agents (monitors, auditors)
- Valeant Pharmaceuticals (maker of tolcapone)
- Western Institutional Review Board® (WIRB®)
- Other collaborating institutions

Once your protected health information has been disclosed it is possible that anyone who receives that information may re-disclose it. Because some of these individuals who receive your protected health information may not be required by law to keep your information confidential, we cannot guarantee that your information will not be released or made available to another party once it leaves Spectrum Health. Therefore, we share your information only if necessary and we use all reasonable efforts to request that those individuals who receive your information take steps to protect your privacy.

How long will my health information be used?

This authorization has no expiration date.

Can I stop my protected health information from being collected?

You can tell us to stop collecting health information that can be traced to you at any time. We will stop, except in very limited cases if needed to comply with law, protect your safety, or make sure the research was done properly. If you have any questions about this please ask.

If you want us to stop, you must tell us in writing. Write or email:

Dr. Jessica Foley, MD

[redacted]

What happens if I do not want you to collect and release my information?

If you decide not to authorize release of your health information as part of this study, your decision will in no way affect your medical care or cause you to lose any benefits to which you are entitled. You cannot participate in this research study if you do not authorize the use or release of your PHI.

When will it be destroyed?

We do not know when your information will no longer be used. Therefore, the information will be kept for an indefinite length of time.

ADDITIONAL OPTIONAL TUMOR BIOLOGY CONSENT

There are optional biology tests that you may agree to participate in if you wish. These include blood samples, extra bone marrow samples, and extra tumor samples. These samples may be collected during routine procedures while you are in the study, and will be used for research tests and studies that will not directly impact your treatment. These research tests and studies may benefit future children with neuroblastoma, medulloblastoma, or other tumors.

If you agree to allow your samples to be used for these future research tests, your samples will be stored in a safe and confidential laboratory area indefinitely. Neither your name nor any other information that identifies you will be used to identify your sample when they are stored in the lab. The samples will be identified only by a unique, de-identified code. Samples will be frozen and stored in a carefully controlled deep freezer. The samples that are stored for future research may only be used by Dr. Sholler and the other investigators who are participating in this study or other NMTRC studies. No information that identifies you will be used for any of these future research tests and studies.

You have the option to remove the samples from the laboratory at any time. In the future, if you ask that your stored samples be destroyed, it is important to know that any research that has already been done on the samples cannot be changed. No matter what you decide to do, it will not affect the care that you will get.

There is no way to predict exactly what research tests will be performed with the stored samples. Because these tests are for research only, usually your study doctor or you will not know the results. It is very unlikely that the research testing might find important information about your current or future health. If this unlikely event happens, the researchers may contact your primary treating oncologist about what the research test results might mean. Only your primary treating oncologist will be notified and the information will not become part of your medical record. Your primary treating oncologist may discuss this unexpected finding with you, and may recommend that you see a genetic counselor and/or repeat testing in a clinical (not research) laboratory if needed. It is possible that your primary treating oncologist may decide that no action is needed.

Future research tests will be looking at genetic information collected from the samples you provide. A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways: Health insurance companies and group health plans may not request your genetic information that we get from this research. Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums. Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA does not prohibit discrimination on the basis of an already manifest genetic disease or disorder.

1. I agree that additional blood samples may be taken and sent to an NMTRC laboratory for biological correlates and additional studies.

   #3: Yes_____ No_____ _____ / _____
   Initials Date

2. I agree that extra bone marrow may be taken and sent to an NMTRC laboratory for additional studies.

   #4: Yes_____ No_____ _____ / _____
   Initials Date

3. If I have a standard of care tumor extraction, extra tumor samples may be taken and sent to an NMTRC laboratory for additional studies.

   #5: Yes_____ No_____ _____ / _____
   Initials Date

4. I agree to let researchers store material (e.g., leftover blood, bone marrow, cells or genetic material that is taken at the time of a procedure) for future use to learn about, prevent, or treat cancer.

   #6: Yes_____ No_____ _____ / _____
   Initials Date

Signature Block for Capable Adult: Long Form

Your signature below documents your permission to take part in this research and to the use and disclosure of your protected health information. You will receive a signed copy of this complete form.

Signature of participant	Date
Printed name of participant	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	

Signature Block for Children

Your signature below documents your permission for the child named below to take part in this research and to the use and disclosure of this child's protected health information. You will receive a signed copy of this complete form.

Printed name of child

Signature of parent or guardian	Date
Printed name of parent or guardian	❑ Parent ❑ Guardian (See note below)

Note on permission by guardians: An individual may provide permission for a child only if that individual can provide a written document indicating that he or she is legally authorized to consent to the child's general medical care. Attach the documentation to the signed document.

Signature of person obtaining consent and assent (if child is 13-17 years old, assent is required)	Date
Printed name of person obtaining consent and assent (if child is 13-17 years old, assent is required)	

Assent

- ❑ Verbal Assent Obtained
- ❑ Not obtained because the capability of the child is so limited that the child cannot reasonably be consulted.

Signature Block for Non-English Speaking: Short Form

Your signature below documents your permission to take part in this research and to the use and disclosure of your protected health information. You will receive a signed copy of this complete form.

Printed name of participant	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	

I certify, to the best of my ability, that an oral presentation was interpreted fully and accurately by the Spectrum Health appointed medical interpreter in the participant's stated primary language, and that I was present for the entire informed consent discussion.

Signature of Witness to Informed Consent Presentation	Date
Printed name of Witness to Informed Consent Presentation	